Exhibit D

Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery

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Purpose: We prospectively evaluated the histological inflammatory response to the large polypropylene transvaginal mesh used for pelvic organ prolapse surgery.

Materials and Methods: Ten patients and 8 controls underwent vaginal punch biopsy sampling before surgery and patients also underwent it 1 year after pelvic reconstructive surgery using polypropylene mesh. Foreign body response to the mesh was assessed using a combination of histological, semiquantitative and computerized image based analysis.

Results: Compared to preoperative histology there was a significant postoperative increase in macrophage and mast cell counts ($p = 0.03$ and 0.01) but no significant changes in the count of cells involved primarily in the infectious cell response or collagen density and the elastin area fraction at the mesh-tissue interface ($p = 0.2$ and 0.3, respectively). Three cases of mild granuloma formation and 2 of mild erosion were observed. There was no significant change in epithelial thickness when comparing preoperative and postoperative samples.

Conclusions: When used for pelvic reconstructive surgery, macroporous monofilament polypropylene mesh induces a mild but persistent foreign body reaction.

Key Words: urethra, prolapse, foreign-body reaction, suburethral slings, polypropylenes

Abbreviations and Acronyms

DP = dermal papilla

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Study received Karolinska Institutet research ethics committee approval.

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THE main rationale for using biomaterials for pelvic reconstructive surgery is a presumed decrease in surgical failure compared to traditional suture repair.[1] Despite the widespread use of synthetic and biological implants for pelvic organ prolapse repair safety information is in short supply.[2] The unique vaginal microenvironment, dynamics, biochemical exchange and immunological response prevent the inference of results from other areas of biomaterial use, such as inguinal hernia surgery, to the pelvic floor.[3]

Macroporous polypropylene mesh has shown clinical efficacy and tissue friendly qualities when used for stress urinary incontinence surgery[4] and it has been associated with a beneficial tensiometric profile in experimental settings.[5] As a result, most synthetic biomaterials that are currently marketed for pelvic organ prolapse surgery are made of monofilament, macroporous polypropylene mesh. An understanding of biocompatibility and the pathophysiological response to polypropylene mesh in urogynecological surgery mainly derives from studies of tension-free mid urethral tapes and laboratory animal studies.[6] However, to our knowledge it remains unknown to what extent the

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increased biomaterial load of large polypropylene mesh influences biocompatibility and the magnitude of the histological response when used in the human vagina.

In the current in vivo study we prospectively evaluated the microscopic inflammatory cell response to large polypropylene transvaginal mesh used in a clinical setting. We present 1-year histological outcomes combined with a macroscopic inflammatory assessment following pelvic reconstructive surgery using a standardized surgical device with macroporous monofilament polypropylene mesh.

MATERIALS AND METHODS

The study was approved by the Karolinska Institutet research ethics committee. Prospective recruitment of patients scheduled for pelvic organ prolapse surgery using transvaginal mesh was initiated in October 2006. Ten consecutive patients undergoing pelvic organ prolapse surgery using the Prolift® system and 8 controls undergoing elective gynecological surgery for other benign indications were included in the study. Table 1 lists patient and control characteristics. In patients clinical examination and biopsy sampling were performed at baseline and 1 year after surgery, whereas controls underwent clinical examination and biopsy sampling only at baseline.

Study inclusion criteria were stage 2 or greater pelvic organ prolapse, as determined with the patient supine using the validated Pelvic Organ Prolapse Quantification system,[7] patient ability to provide informed consent to participate, physical and mental capability of participating in followup and no exclusion criteria. Study exclusion criteria were previous pelvic organ cancer, severe rheumatic disease, systemic steroid treatment, connective tissue disorders and physical or mental incapability of participating in followup or providing informed consent to participate in the study. Exclusion criteria in controls were identical to those in patients but also included pelvic organ prolapse and stress urinary incontinence.

Table 1. *Descriptive group characteristics*

	Pts	Controls	p Value*
No. participants	10	8	
Mean ± SD age	67.1 ± 7.5	42 ± 13.0	0.002
Median parity (range)	2.5 (1–4)	1.3 (0–2)	0.06
Mean ± body mass index (kg/m^2)	26.5 ± 4.8	23.6 ± 4.0	0.5
No. menopause (%)	10 (100)	2	<0.001
No. hormone replacement therapy (%)	4 (40)	0	0.07
No. local estrogen (%)	3 (30)	0	0.1
No. smoking (%)	0	0	1.0
No. Prolift (%):			
Anterior	4 (40)	—	Not applicable
Posterior	2 (20)	—	Not applicable
Anterior + posterior	4 (40)	—	Not applicable

* Comparisons of nonparametric data were done using the Mann-Whitney U test and of proportions using the chi-square test.

Commercial trocar guided mesh kits were used. The uniformly sized and shaped macroporous monofilament polypropylene mesh was passed through the obturator foramen and arcus tendineus fascia pelvis using 4 trocar guided extension arms in the anterior vaginal compartment.[8] In the posterior compartment the mesh was positioned using a trocar guided transgluteal approach and the 2 extension arms were passed through the sacrospinous ligament.[8] After optimal placement the mesh was covered by vaginal mucosa using an uninterrupted suture line of delayed absorbable polyglactin 910.

Before surgery all patients underwent macroscopic grading of the clinical inflammatory response on an ordinal scale.[9] Using a grading system of 0—none, 1—mild, 2—moderate, 3—pronounced and 4—severe certain clinical parameters were assessed, including granuloma, erosion, necrosis, infection and rejection. The macroscopic inflammatory grading system proved to be reliable, easy to use and consistent with histopathological assessments in a previous study of biomaterials for pelvic organ prolapse surgery.[10]

At surgery a 6 mm wide and 10 mm deep punch biopsy was done from the anterior or posterior vaginal wall depending on mesh positioning using standardized sampling techniques that have been previously described in detail.[10] The biopsy site was based on the standardized dimensions of the polypropylene mesh and it was estimated to include the mesh-tissue interface. One year after surgery at the outpatient clinic a second 6 mm punch biopsy was obtained from the same location at a position estimated to be adjacent to the mesh-tissue interface after administering local anesthesia, consisting of 5 ml 0.25% Marcaine® plus epinephrine using identical sampling techniques. The biopsy site was estimated according to knowledge of the standardized mesh placement and dimensions, and in some patients by palpating the mesh before sampling.

Biopsies were immediately immersed in 4% neutral buffered formaldehyde solution, after which they were dehydrated and embedded in paraffin. Specimens were cut into sections of a nominal thickness of 5 μm and for each biopsy 2 specimens were prepared. The first specimen was stained with hematoxylin and eosin for cell and collagen analysis, and the second specimen was unstained for elastin analysis.

Computer assisted morphometric analysis was performed to quantify total cell content in the subepithelial connective tissue. Images were captured with a Sony® DXC-9100P 3-chip charge coupled device color camera mounted on an Axioplan™ 2 light microscope. Images were analyzed using the MicroGOP 2000s image analysis software (Context Vision AB, Linköping, Sweden) installed in SUN SPARCstation™ 20 computer workstation. After processing, an unbiased counting frame with an area of 50,000 μm^2 was superimposed on the image[11] and 3 measurements were made in every specimen to calculate the numerical density of cells per μm^2. Using the same computer workstation epithelial measurements were made after creating a binary epithelial profile of the images.[12] Epithelial measurements included epithelial height (the distance from the basement layer to the sur-

face), the distance from the top of the DPs to the epithelial surface, DP width and the distance between the DP tops.

Manual cell counts in the subepithelial connective tissues were subsequently performed in every specimen to assess the number of fibroblasts, macrophages, monocytes, granulocytes, lymphocytes, plasma cells and mast cells. Specimens were placed in the microscope under the 100× oil immersion objective for counting. For each specimen 200 cells were counted. Semiquantitative grading was performed to assess the severity of overall inflammation and vasculitis as well as collagen density. Semiquantitative grading of inflammation and vasculitis consisted of a 5-step ordinal scale of none, mild, moderate, pronounced and severe. Collagen density was graded as loose, fairly dense, moderately dense or very dense. All histological examinations were performed by a single pathologist blinded to clinical outcome.

The elastin area fraction was analyzed using a Neofluor optical lens (Carl Zeiss, Jena, Germany) and fluorescent light in the same microscope, as described. Specimens were placed in the microscope under the 40× objective and illuminated with ultraviolet light using a filter range of 450 to 500 nm to detect autofluorescence signals from the elastic fibers. Three uniformly sampled images per section were captured, digitized and stored in the computer. For all specimens a reference area of 54,162 μm^2 was used for all images captured and each image consisted of 512 × 512 pixels. Image analysis software was then used to calculate the area fraction of the elastic fibers as a percent in each specimen by dividing total elastic fiber area by the total tissue area on the 3 images.[13]

Data on descriptive characteristics are presented as percents. Comparisons between proportions were performed using the chi-square test. For dependent samples comparisons of nonparametric data were performed using the Wilcoxon signed rank test. For independent sample comparisons the Mann-Whitney U test was used. Significance was considered at $p < 0.05$ in all analyses. All testing was performed on a statistical group level using Statistica (StatSoft®).

RESULTS

Table 2 lists the outcomes of histological and semiquantitative analyses. One preoperative patient biopsy could not be assessed due to a lack of epithelium. Compared to preoperative histology there was a significant increase in macrophage and mast cell counts 1 year postoperatively ($p = 0.03$ and 0.01, respectively). There were no significant changes in the semiquantitative assessment of inflammatory cell infiltration and vasculitis when comparing preoperative and postoperative grading ($p = 0.2$ and 1.0, respectively), although the average inflammatory cell infiltration increased. Cells involved primarily in the humoral immune response, including monocytes, granulocytes, lymphocytes and plasma cells, did not change significantly at the postoperative assessment compared to preoperative counts.

Postoperatively the total cell count decreased significantly compared with preoperative counts ($p = 0.02$), as did the number of fibroblasts ($p = 0.04$). However, there were no significant differences between preoperative and postoperative assessments of collagen density and the elastin area fraction at the mesh-tissue interface ($p = 0.2$ and 0.3, respectively).

Baseline histological counts and morphological grading in patients and controls were similar in all respects except total cell count, the elastin fraction and inflammatory cell infiltration (figs. 1 and 2). Patients had a higher elastin area fraction and a lower total cell count than healthy controls ($p = 0.006$ and 0.05, respectively). With regard to baseline semiquantitative inflammatory cell infiltration controls had significantly higher expression than patients.

There were no statistically significant changes in macroscopic inflammatory grading assessment postoperatively, although granuloma formation and erosion were observed (table 3). Three cases of mild granuloma formation and 2 of mild erosion were detected but neither resulted in any surgical interventions. There were no cases of serious mesh related complications or mesh exposure/rejection.

Compared to the baseline assessment and to matched controls there were no significant differences in epithelial characteristics 1 year after sur-

Table 2. *Histological analysis and comparison*

	Mean ± SD No.			p Value	
	Controls	Preop Pts	Postop Pts	Preop Pts vs Controls (Mann-Whitney U test)	Preop vs Postop Pts (Wilcoxon signed rank test)
No. participants	8	9	10		
Total cell count/μm^2	0.0004 ± 0.0001	0.0003 ± 0.00005	0.0002 ± 0.00006	0.05	0.02
Fibroblasts (%)	166.8 ± 10.7 (83.4)	170 ± 11.5 (85.0)	159.3 ± 12.6 (79.7)	0.5	0.04
Macrophages (%)	3.4 ± 3.0 (1.7)	3.78 ± 2.6 (1.9)	6.2 ± 4.2 (3.1)	0.6	0.03
Monocytes (%)	1.6 ± 1.3 (0.8)	2.11 ± 1.4 (1.1)	2.1 ± 1.5 (1.1)	0.5	1.0
Granulocytes (%)	0.5 ± 0.8 (0.25)	0.44 ± 1.0 (0.2)	0.4 ± 0.7 (0.2)	0.6	0.9
Lymphocytes (%)	26.0 ± 8.8 (13)	21.22 ± 9.1 (10.6)	25 ± 9.64 (12.5)	0.3	0.4
Mast cells (%)	1.6 ± 1.9 (0.8)	2.33 ± 1.4 (1.2)	7 ± 4.47 (3.5)	0.3	0.01
Plasma cells (%)	0.1 ± 0.4 (0.07)	0.11 ± 0.3 (0.1)	0 ± 0	0.9	1.0
Cell types (%)	200 (100)	200 (100)	200 (100)		

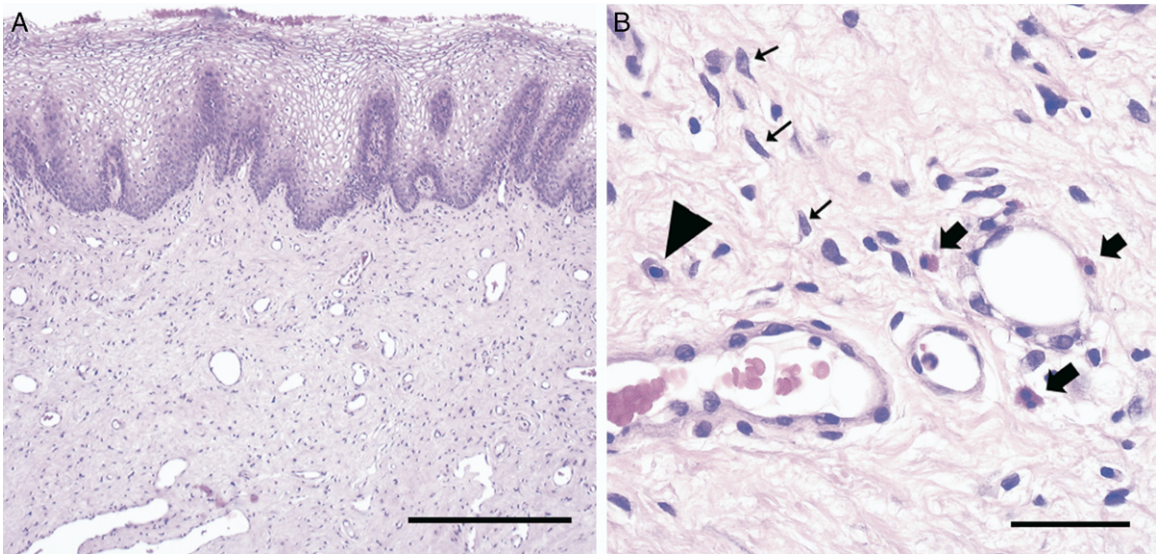

Figure 1. Control specimen. *A,* low magnification shows numerous connective tissue papillae at epithelial-connective tissue junction. H & E. Scale bar indicates 500 μm. *B,* high magnification demonstrates connective tissue. Note 3 arterioles at center. Arrowhead indicates macrophage. Thick arrows indicate eosinophilic granulocytes. Thin arrows indicate fibroblasts. H & E. Scale bar indicates 50 μm.

gery using polypropylene mesh (table 4). Epithelial thickness, DP height and width, and the distance between the DPs showed little variation at 1 year of followup.

DISCUSSION

Significant foreign body reactions and poor tissue integration have previously been described for polyethylene, polytetrafluoroethylene and multifilament polypropylene mesh when used as sling materials for stress urinary incontinence.[4] In contrast, macroporous monofilament polypropylene mesh has been shown not to induce severe inflammatory reactions with a limited adverse influence on paraurethral connective tissue metabolism when used for the tension-free vaginal tape procedure.[4]

It is to be expected that the introduction of foreign material in human tissues results in some degree of host-foreign body reaction[14] but to our knowledge this is the first human in vivo study to assess the inflammatory response to large polypropylene mesh for pelvic reconstructive surgery. Previous studies of the biocompatibility of new prosthetic materials intended for urogynecologic surgery were mostly performed in mice and rats.[15] However, rodent immunology may differ substantially from that in humans and the appropriateness of transferring data on biocompatibility between species is questionable. Therefore, human in vivo studies are essential to evaluate biocompatibility for the intended use in the anatomical region and in patients, although such studies are often limited by a relatively small number of participants.

In the current study there was a significant postoperative increase in the number of macrophages and mast cells compared with preoperative counts. These cell types are key mediators involved in the human foreign body immune reaction and they are normally scattered throughout the subepithelial connective tissues of the vagina. The modus operandi of macrophages includes phagocytosis, antigen presentation and chemokine secretion. Mast cells primarily act by degranulation of inflammatory and chemotactic substances, such as histamine, as a response to antigen triggering. Moderately increased postoperative counts of macrophages and mast cells 1 year after surgery suggest that large polypropylene mesh activates an enduring but nonsevere cellular foreign body response in human vaginal submucosal tissue.

Further evidence of a mild inflammatory response was provided by semiquantitative inflammatory cell infiltration grading, which also increased postoperatively, although in statistically nonsignificant fashion. While the results of animal studies should not be applied to humans, these combined results are in agreement with laboratory rabbit and rat models suggesting that macroporous monofilament polypropylene mesh induces a mild suburethral foreign body reaction when used for incontinence surgery.[16] Our data also indicate that the postoperative histological tissue reaction was of a noninfectious type since postoperative counts of cells involved primarily in the infectious immune defense, such as lymphocytes, were unaltered.[17] Epithelial thickness and DPs are influenced by hormones and local inflammatory conditions, although no significant

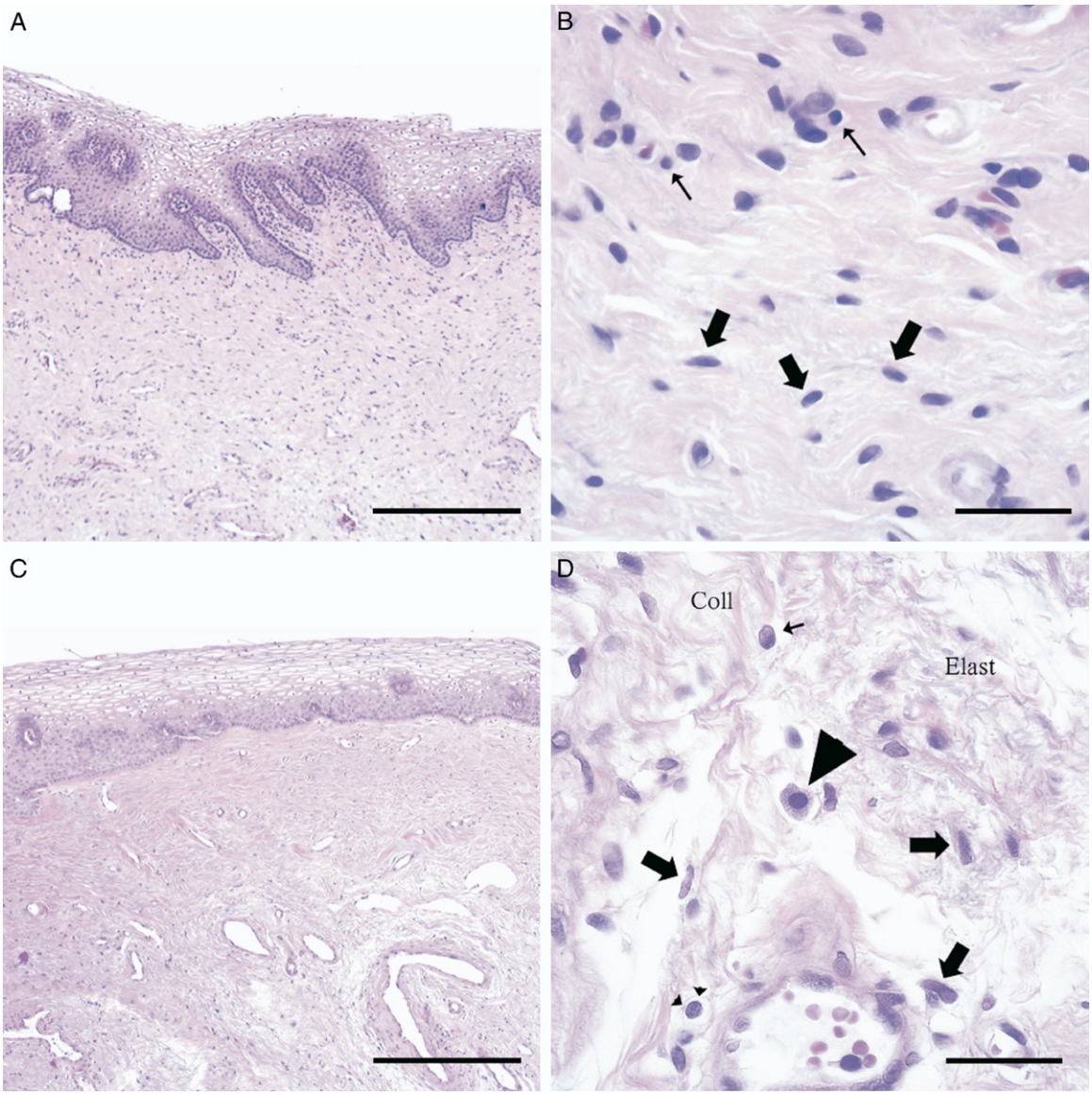

Figure 2. Patient specimen. *A*, low magnification of preoperative specimen shows numerous connective tissue papillae, similar to those in control. *B*, high magnification of preoperative specimen. Thick arrows indicate fibroblasts. Thin arrows indicate lymphocytes. *C*, low magnification of postoperative specimen reveals connective tissue papillae that are not so prominent. *D*, high magnification of postoperative specimen demonstrates curliness and pinkish color of collagen fibers *(Coll)* and more grayish-bluish color of elastic fibers (*Elast*). Large arrowhead indicates mast cell. Thick arrows indicate fibroblasts. Thin arrow indicates lymphocyte. H & E. Scale bar indicates 500 (*A* and *C*) and 50 (*B* and *D*) μm.

epithelial changes were observed after 1 year compared to baseline and controls. This corroborates the overall histopathological impression as well as the macroscopic inflammatory grading of a low intensity inflammatory foreign body response.

Slight but significant decreases in total cell and fibroblast counts were observed postoperatively, suggesting that as anticipated the acute and intermediate phases of healing and scar formation were completed by the time of biopsy sampling. We found no signs of an adverse influence on connective tissue metabolism adjacent to the mesh 1 year after surgery, where the elastin area fraction and collagen density were similar to preoperative assessments. However, tissue integration of the mesh could not be assessed directly since biopsy sampling from the mesh was avoided, so as not to trigger an implant infection that might have provoked erosion. Elastin is an abundant protein in connective tissues, especially where there is a need for recoil, as in the vagina. A higher elastin area fraction in patients with pelvic organ prolapse compared to controls supports the notion of a role for elastin in the etiology of pelvic organ prolapse.[18] It is also possible that the

Table 3. *Semiquantitative results, image analysis and macroscopic assessment*

				p Value	
	Controls	Preop Pts	Postop Pts	Preop Pts vs Controls (Mann-Whitney U test)	Preop vs Postop Pts (Wilcoxon signed rank test)
No. participants	8	9	10		
Semiquantitative results + image analysis:					
Median inflammatory cell infiltration (range)*	1.5 (0–4)	0 (0–0)	0.5 (0–3)	0.02	0.2
Median vasculitis (range)*	0 (0–0)	0 (0–0)	0 (0–0)	0.2	1.0
Median collagen density (range)*	3 (1–3)	2.5 (2–3)	2 (0–3)	0.4	0.2
Mean ± SD % elastin area fraction	3.18 ± 3.67	8.61 ± 2.64	7.52 ± 3.75	0.006	0.3
Macroscopic inflammatory grade (compartment):					
Anterior	No inflammatory reaction	No inflammatory reaction	Mild granuloma (3 pts), mild erosion (1)	Not applicable	0.2
Middle	No inflammatory reaction	No inflammatory reaction	Mild granuloma (2 pts), mild erosion (1)	Not applicable	0.2
Posterior	No inflammatory reaction	No inflammatory reaction	Mild granuloma (3 pts)	Not applicable	0.5

* Graded as 0—none, 1—mild, 2— moderate, 3—pronounced and 4—severe.

observed difference in elastin area fraction, total cell count and inflammatory cell infiltration was simply a result of differences in patient and control characteristics, such as age and menopausal status.

Despite the mentioned differences in characteristics there were no significant differences in specific inflammatory cell counts when comparing patients to controls at baseline. Thus, it is biologically plausible that the persistent postoperative increase in macrophage and mast cell counts could be attributable to the mesh. The supposition of a causal association concurs with the results of other reports[16,19] and it is further strengthened by the unbiased assessment of the histopathologist, who was blinded to clinical outcome. For ethical reasons healthy controls did not undergo repeat biopsy.

The low grade histological inflammatory response after transvaginal mesh surgery was in agreement with macroscopic clinical inflammatory grade. Inflammatory reactions on visual assessment were predominantly noted as mild granuloma formation. Two cases of mild erosion were also observed but neither resulted in any surgical intervention. The combined results of the clinical and histological inflammatory evaluation suggest that biocompatibility was satisfactory. Nonetheless, it is important to recognize that a larger study population with transvaginal mesh surgery would undoubtedly generate an increased number of mesh related complications. Clinicians and patients should be aware of the possibility of late mesh related inflammatory reactions when using a large polypropylene mesh.

Future studies are necessary to determine whether decreasing the polypropylene bioload by mixing or coating the polypropylene filaments with absorbable biomaterials, such as polyglactin 910 (composite mesh), would also decrease the histological response.[20]

CONCLUSIONS

Our study demonstrates that large macroporous monofilament polypropylene mesh induces a mild but persistent histological foreign body reaction when

Table 4. *Epithelial measurements in patients and controls*

	Mean ± SD (μm)			p Value	
	Controls	Preop Pts	Postop Pts	Preop Pts vs Controls (Mann-Whitney U test)	Preop vs Postop Pts (Wilcoxon signed rank test)
No. participants	8	9	10		
Basement layer–surface	436.2 ± 160.6	398.6 ± 127.5	431.6 ± 172.4	0.6	0.8
DP top–surface	317.5 ± 132.2	301.7 ± 114.9	320 ± 165.8	0.9	0.9
DP width	171.9 ± 233.7	66.1 ± 19.7	119.7 ± 73.5	0.3	0.4
Between DP tops	293.4 ± 140.4	316.7 ± 357.1	693.7 ± 571.7	0.2	0.4

used for pelvic organ prolapse surgery. Our findings provide a biological rationale for the development of noninfectious mesh erosion after transvaginal pelvic organ prolapse surgery using polypropylene mesh.

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